

Dear Editor,

Thank you very much for your comments and advices.

We have carefully revised the manuscript in accordance with the reviewers' comments. Moreover, this manuscript has been polished by a native English speaker.

Then, we would like to resubmit the revised manuscript entitled "PPARGC1A rs8192678 G>A polymorphism affects the severity of hepatic histological features and NASH in patients with NAFLD" (NO.64071) for your further consideration.

Additionally, point by point responses are listed below.

Sincerely yours,

Jian-Gao Fan, MD, PhD

Center for Fatty Liver, Department of Gastroenterology, Xinhua Hospital Affiliated to Shanghai Jiao Tong University School of Medicine, Shanghai Key Lab of Pediatric Gastroenterology and Nutrition, 1665 Kong Jiang Road, Yangpu District, Shanghai 200092, China.

Tel./Fax: +86-21-25077340

Email address: fanjiangao@xinhumed.com.cn.

Replied to Reviewer:

Minor comments:

I read with great interest this manuscript, Peroxisome proliferator-activated receptor- γ coactivator-1 α rs8192678 affects the severity of hepatic histological features and NASH in patients with NAFLD. I commend the authors for a well designed study. I found the study interesting and important given the lack of clear data with this topic. In general, I find the manuscript well written. However, the abstract makes its conclusions in a much strong fashion than the paper itself and I feel the conclusions should be softened due to the limitations the authors identify. The one aspect of the paper than needs more discussion is the role of the AA genotype. This is mentioned in a few sections that the AA genotype was not associated with NAFLD. Given the small sample size an explanation of this relationship needs to be better described.

Answer: We thank the reviewer for the comment. The conclusion part in abstract was revised to soften the conclusion in this article. In our study, we found the PPARGC1A rs8192678 risk A allele (GA+AA genotypes) was associated with NAFLD, and also with S2-3, A \geq 2 and NASH in NAFLD patients, which might also associate with nonobese NASH. And we also realized the limitations in our study, therefore, in further studies, a large number of patients with liver biopsy-proven NAFLD should be included, and well-designed case-control studies should be performed to confirm and support these findings.

And in our study, we found the variation of PPARGC1A rs8192678 GA genotype was significantly higher in patients with NAFLD, but AA genotype showed no difference between NAFLD and control groups, which was consistent with the findings of *Lin et al.* in obese children in Taiwan (Lin et al, Am J Clin Nutr, 2013). The probable reasons were analyzed in Lin's study as follows. First, the number of homozygous mutants (AA genotype) in the NAFLD group is relatively small. The nonsignificance could be due to sample variation and inadequate statistical power. Second, the cellular effects of PGC-1 α are not simple. The exact mechanisms by which PGC-1 α influences the pathogenesis of fatty liver remain unclear. PGC-1 α may

be involved in different pathways that either increase or reduce fat accumulation. In this case, it is possible that the effect of homozygous mutants (AA genotype) may not be higher than that of heterozygotes (GA genotype). In our study, the percentage of PPARGC1A rs8192678 AA genotype was only 13.56% (8/59) in NAFLD patients, but the GA genotype was reached to 62.71% (37/59). The reasons were also discussed in our study in the discussion part. And in further study, large number of NAFLD patients should be enrolled, even in different ethnic groups, and the function research of PPARGC1A also might be carried out.